

5 WHAT IS CLAIMED IS:

1. An oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the amount of antagonist released from said dosage form after tampering to the amount of said antagonist released from said intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C wherein said agonist and antagonist are interdispersed and are not isolated from each other in two distinct layers.

2. An oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the amount of antagonist released from said dosage form after tampering to the amount of said antagonist released from said intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C wherein said antagonist is in the form of multiparticulates individually coated with a sequestering material which substantially prevents release of the antagonist.

3. An oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the amount of antagonist released from said dosage form after tampering to the amount of said antagonist released from said intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C wherein said antagonist is dispersed in a matrix comprising a sequestering material which substantially prevents the release of the antagonist.

- 5 4. An oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a
sequestered opioid antagonist which is substantially not released when the dosage
form is administered intact, such that the ratio of the amount of antagonist contained
in said intact dosage form to the amount of said antagonist released from said intact
10 dosage form after 1 hour is about 4:1 or greater, based on the in-vitro dissolution at 1
hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II
(paddle) apparatus at 75 rpm at 37 degrees C wherein said agonist and antagonist are
interdispersed and are not isolated from each other in two distinct layers.
- 15 5. An oral dosage form comprising (i) an opioid agonist in a releasable form; and (ii) a
sequestered opioid antagonist which is substantially not released when the dosage
form is administered intact, such that the amount of antagonist released from said
intact dosage form after 1 hour is less than an amount bioequivalent to 0.25 mg
naltrexone and the amount of said antagonist released after 1 hour from said dosage
20 form after tampering is an amount bioequivalent to 0.25 mg naltrexone or more, said
release based on the dissolution at 1 hour of said dosage form in 900 ml of Simulated
Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C,
wherein said agonist and antagonist are interdispersed and are not isolated from each
other in two distinct layers.
- 25 6. An oral dosage form comprising (i) an opioid agonist in a releasable form; and (ii)
sequestered naltrexone or a pharmaceutically acceptable salt thereof which is
substantially not released when the dosage form is administered intact, such that the
amount of naltrexone released from said intact dosage form after 1 hour is less than
0.25 mg and the amount of said naltrexone released after 1 hour from said dosage
30 form after tampering is 0.25 mg or more, said release based on the dissolution at 1
hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II
(paddle) apparatus at 75 rpm at 37 degrees C, wherein said agonist and naltrexone are
interdispersed and are not isolated from each other in two distinct layers.
- 35 7. An oral dosage form comprising (i) a therapeutic effect of an opioid agonist; and (ii) a
sequestered opioid antagonist, such that at 1 hour after oral administration, said
dosage form releases not more than 25% of said antagonist, said dosage form

- 5 providing analgesia and said released antagonist not affecting analgesic efficacy,
wherein said agonist and antagonist are interdispersed and are not isolated from each
other in two distinct layers.
- 10 8. An oral dosage form comprising: (i) an opioid agonist in a releasable form; and an (ii)
opioid antagonist in substantially non-releasable form wherein said antagonist is in the
form of multiparticulates individually coated with a material that substantially
prevents release of the antagonist.
- 15 9. An oral dosage form comprising: (i) an opioid agonist in a releasable form; and an (ii)
opioid antagonist in substantially non-releasable form wherein said antagonist is
dispersed in a matrix comprising a material that substantially prevents the release of
the antagonist.
- 20 10. The oral dosage form of claims 1-4 wherein said ratio is 10:1 or greater.
11. The oral dosage form of claims 1-4 wherein said ratio is 50:1 or greater.
12. The oral dosage form of claims 1-4 wherein said ratio is 100:1 or greater.
- 25 13. The oral dosage form of claim 6 wherein said intact dosage form releases at least
0.025 mg naltrexone at 1 hour.
14. The oral dosage form of claims 1-5 and 7-9 wherein said intact dosage form provides
at least an amount of antagonist bioequivalent to 0.025 mg naltrexone at 1 hour.
- 30 15. The oral dosage form of claim 5 wherein the amount of antagonist released after 1
hour from said tampered dosage form is an amount bioequivalent to 0.5 mg naltrexone
or more.
- 35 16. The oral dosage form of claims 5 and 15 wherein the amount of antagonist released
after 1 hour from said intact dosage form is an amount bioequivalent to 0.125 mg
naltrexone or less.

5

17. The oral dosage form of claim 6 wherein the amount of antagonist released after 1 hour from said tampered dosage form is 0.5 mg naltrexone or more.

10

18. The oral dosage form of claims 6 and 17 wherein the amount of antagonist released after 1 hour from said intact dosage form is 0.125 mg naltrexone or less.

15

19. The oral dosage form of claims 1-9, wherein the opioid agonist is selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone, oxymorphone, buprenorphine, fentanyl and derivatives thereof, dipipanone, heroin, tramadol, etorphine, dihydroetorphine, butorphanol, levorphanol, pharmaceutically acceptable salts thereof and mixtures thereof.

20

20. The oral dosage form of claim 19, wherein the opioid agonist is selected from the group consisting of oxycodone, hydrocodone and pharmaceutically acceptable salts thereof.

25

21. The oral dosage form of claims 1-5 and 7-9, wherein the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.

30

22. The oral dosage form of claim 21, wherein the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, pharmaceutically acceptable salts thereof and mixtures thereof.

35

23. The oral dosage form of claim 22, wherein the opioid antagonist comprises naltrexone or a pharmaceutically acceptable salt thereof.

24. The oral dosage form of claims 2 and 8, wherein the material comprises a cellulose polymer or an acrylic polymer that is insoluble in the gastrointestinal tract and impermeable to the opioid antagonist contained within the coating.

- 5 25. The oral dosage form of claim 24, wherein the cellulose polymer is selected from the group consisting of ethylcellulose, cellulose acetate, cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, and mixtures thereof.
- 10 26. The oral dosage form of claim 24, wherein the acrylic polymer is selected from the group consisting of acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer,
- 15 polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.
- 20 27. The oral dosage form of claims 1-9, wherein the dosage form provides sustained-release of the opioid agonist.
28. The oral dosage form of claim 27, wherein the dosage form is a sustained-release tablet or a sustained-release capsule.
- 25 29. The oral dosage form of claim 2 and 8 wherein said multiparticulates are in the form of inert beads coated with said antagonist and overcoated with said material.
- 30 30. The oral dosage form of claims 2 and 8 wherein said multiparticulates are in the form of a granulation comprising said antagonist and said material.
31. The oral dosage form of claims 2 and 8 wherein said multiparticulates are dispersed in a matrix comprising said opioid agonist.
32. The oral dosage form of claims 2 and 8 wherein said multiparticulates are contained in a capsule with said opioid agonist.
- 35 33. The oral dosage form of claims 3 and 9 wherein said matrix is in the form of pellets.

- 5 34. The oral dosage form of claim 33 wherein said pellets are dispersed in a matrix comprising said opioid agonist.
35. The oral dosage form of claim 33 wherein said pellets are contained in a capsule with said opioid agonist.
- 10 36. The oral dosage form of claims 1-9 wherein said tampering is by crushing.
37. The oral dosage form of claim 27 wherein said tampering is in a manner as to obtain an immediate release of said agonist.
- 15 38. The oral dosage form of claims 1-9 wherein said tampering is to make the agonist available for inappropriate use.
39. The oral dosage form of claims 1-9 wherein said antagonist does not significantly affect analgesia provided by the agonist.
- 20 40. A method of decreasing the abuse of an opioid agonist in an oral dosage form, comprising incorporating said opioid agonist into a dosage form of claims 1-9.
- 25 41. A dosage form comprising:
 (a) an opioid agonist; and
 (b) naltrexone in a substantially non-releasable form; wherein the agonist and naltrexone are at least partially interdispersed.
- 30 42. The dosage form of claim 41 wherein the opioid agonist is oxycodone, codeine, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, salts thereof, or mixtures thereof.
43. The dosage form of claim 42 wherein the opioid agonist is oxycodone hydrochloride.
- 35 44. The dosage form of claim 42 wherein the opioid agonist is hydrocodone bitartrate.

- 5 45. The dosage form of claim 42 wherein the opioid agonist is hydromorphone hydrochloride.
46. The dosage form of claim 41 wherein at least part of the naltrexone is in a matrix.
- 10 47. The dosage form of claim 41 wherein at least part of the naltrexone is in a coated bead.
48. The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 15% by weight of the naltrexone *in vivo* after 36
- 15 hours.
49. The dosage form of claim 48 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 8% by weight of the naltrexone *in vivo* after 36
- 20 hours.
50. The dosage form of claim 49 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 1% by weight of the naltrexone *in vivo* after 36
- 25 hours.
51. The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 3% by weight of the naltrexone *in vivo* after 1
- 30 hour.
52. The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 1.0% by weight of the naltrexone *in vivo* after 1
- 35 hour.
53. The dosage form of claim 41 wherein the naltrexone in a substantially non-releasable form is adapted to release less than 0.5% by weight of the naltrexone *in vivo* after 1
54. A dosage form comprising:

5

(a) an opioid agonist; and

(b) an orally-bioavailable opioid antagonist in a substantially non-releasable form;

10

55. The dosage form of claim 54 wherein the agonist and antagonist are at least partially interdispersed.

56. The dosage form of claim 54 wherein the orally-bioavailable opioid antagonist is naltrexone, or a salt thereof.

15

57. The dosage form of claim 54 wherein the opioid agonist is oxycodone, codeine, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, or salts thereof or mixtures thereof.

20

58. The dosage form of claim 54 wherein at least part of the antagonist is in a matrix.

59. The dosage form of claim 54 wherein at least part of the antagonist is in a coated bead.

25

60. A method of preparing an oral dosage form comprising pretreating an opioid antagonist to render it substantially non-releasable; and combining the pretreated antagonist with a releasable form of an opioid agonist.

61. A method of treating pain comprising administering to a human patient a dosage form of claims 1-9, 41 or 54.